IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 7469
MADGE *et al.*	Art Unit: 1621
Application No.: 10/659,178	Examiner: Yevgeny Valenrod
Filed: September 9, 2003	Atty. Docket: 2451.0090006
For: **Boronic Acid Salts**	

Declaration Under 37 C.F.R. § 1.132 Of Dr. Stephen Philip Marsden

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Stephen Philip Marsden, declare and state as follows:

1. I, Stephen Philip Marsden, am a Reader in Organic Chemistry at the University of Leeds, Leeds, England. I have a B.Sc. in chemistry from Imperial College, London and a Ph.D. from the same Institution. I was a NATO post-doctoral Fellow at Columbia University, New York from 1993 to 1994. I have co-authored several papers in the peer reviewed literature on the preparation and reactions of boronic acid derivatives and was awarded the Meldola Medal of the Royal Society of Chemistry in part for this work. I am therefore fully conversant with the chemistry of boronic acids. A copy of my *Curriculum Vitae* is attached.

2. I was previously a consultant for Trigen Limited, the original assignee, under a remunerated agreement. The application has recently been sold to PAION Deutschland GmbH and I have continued working as a consultant for this latter company. Although my agreement with Trigen Limited was for payment, I was not in fact paid until after the application had been sold to PAION Deutschland GmbH and I am now a paid consultant for PAION.

3. I have reviewed and am familiar with the application as filed, the Preliminary Amendment of 9 March 2005, the restriction requirement of 10 April 2006, the Reply to

Restriction Requirement And Amendment of 10 May 2006, the Office Action of 5 February 2007, the Amendment and Reply of 20 March 2007, the Office Action of 23 May 2007, the Amendment and Reply of 17 August 2007, the Supplemental Amendment and Reply of 26 September 2007, the Declaration of Dr. Anthony Kennedy and attachments, the supplemental Amendment of 31 October 207, and the Office Action of 31 January 2008. I have also reviewed and are familiar with the documents cited by the examiner in the office actions, namely Rewinkel *et al Current Pharmaceutical Design*, 1999, 5, 1043-1075 (hereinafter "Rewinkel"), de Nanteuil *et al*, US Patent No. 5,814,622 (hereinafter de Nanteuil); and Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams"), Lee et al Biochemistry 1997, 36, 13180, and Deadman et al *J. Med. Chem.*, 1995, *38*, 1511-1522 (hereinafter "Deadman").

4. I have also reviewed and am familiar with the document "TRI 50b non-confidential information". This document describes the pinacol ester of a boronic acid identified in the present application as TRI 50c. I understand from this document and from the application that TRI 50c is a thrombin inhibitor and that its ester forms will in effect as prodrugs to release the free acid. The boronic acid 21 identified by the Examiner in Rewinkel is structurally close to TRI 50c. I have further reviewed and am familiar with the documents Wu *et. al., U. Pharm. Sci.* 89: 758 (2000) ("Wu") and International patent publication No WO 02/059130 ("Gupta").

5. I would like to start by summarising those parts of my general knowledge of boronic acid chemistry which seem relevant to the present application. Boronic acids are recognized to be oxidatively unstable and to occur as heterogenous mixtures with their anhydrides. In view of their instability, free boronic acids would not be a good choice for a drug substance. A number of common techniques are known for stabilising boronic acids. I discuss these in the following paragraphs.

6. Perhaps the most common technique is to combine the boronic acid with a strong Lewis base, since Lewis bases are known to form stable adducts, for example diethanolamine adducts are notoriously stable. Another example of a strong Lewis base is the fluoride ion. This will react with a boronic acid $RB(OH)_2$ to form the trifluoroborate salt RBF_3^-. The B-F bond is strong and, because of its electronegativity,

fluorine makes boron a stronger Lewis acid and more prone to form the tetrahedral form, which contributes to stabilisation as I describe below in paragraph 8.

7. Another common method used to stabilise boronic acids is to derivatise them as esters with bulky diols such as pinanediol.

8. The usual mechanism for degradation of a boronic acid is oxidation, which could be by reaction with molecular oxygen or with hydroperoxide anion. In either case, the oxidant species attacks trivalent boron triggering cleavage of the C-B bond. The stabilisation techniques I have discussed in paragraph 6 therefore work by forming tetravalent boron and blocking access to the boron atom by the oxidant species. Bulky ester forming groups would seem to act by disfavouring formation of an adduct with the oxidant on steric grounds.

9. I would like now to discuss the work done on providing Velcade as a stable drug formulation as described in Wu and Gupta. Wu diagrammatically illustrates oxidation both by hydroperoxide and molecular oxygen in accordance with the mechanisms above. Wu shows that the use of strongly basic conditions leads to rapid decomposition of the boronic acid, presumably mediated by hydoperoxide anion. (See Figure 4 of Wu). Gupta describes the stabilisation of the Velcade free acid in the form of a mannitol ester. My interpretation of the advantages of the mannitol ester are that it prevents anhydride formation and provides a steric barrier to oxidation. There may also be some stabilisation by the action of further hydroxyl groups of mannitol as a Lewis base to complex the boron.

10. I have been asked to put myself in the shoes of a chemist tasked with stabilizing boronic acid TRI 50c or Rewinkel's boronic acid 21, taking into account the documents cited by the examiner and my general knowledge of boronic acid chemistry. As outlined in paragraphs 6 to 9, my first thought on either date would have been to use one of the conventional techniques to form a tetrahedral adduct. In particular, I would think of making the diethanolamine adduct. This might prove to be excessively stable (too hard to cleave). If that proved to be the case, the next logical thing would be to put

on a bulky ester forming group, e.g. pinacol or pinanediol, or indeed mannitol as proposed by Gupta.

11. I would discard stabilisation with fluoride for toxicity reasons. Nothing else would have occurred to me as a method for stabilizing TRI 50c.

12. Specifically, it would not have occurred to me to convert TRI 50c or Rewinkel's compound 21 into a base addition salt as described in the present application. I think there are a number of reasons for this. Firstly, I have never read of a boronic acid being isolated as a base addition salt. To my knowledge boronic acids are always sold either as the free acid (recognized to be an impure mixture), as an ester or less frequently as a trifluoroborate salt. I do not regard salt formation as described in Adams as an obvious way of isolating the compound, particularly for the reasons I give in the next paragraph.

13. Hydroxides are used to activate boronic acids for transmetallation reactions. In these transmetallation reactions, a free boronic acid is combined with a transition metal and a hydroxide base. The hydroxide tetracoordinates with the boron, thus weakening the B-C bond and thereby promoting transfer of the organic moiety to the metal. This is a relatively common procedure and I would ask myself why boronic acids are not sold as salts for use in the reaction. In thinking of this, I would bear in mind that the presence of alkali activates peroxide by forming the hydroperoxide anion, as described in Wu and as well known to organoboron chemists. The risk which alkali would present of causing degradation taken together with the observation that boronate salts are, to my knowledge, never sold, despite their apparent commercial attractiveness, would have biased me against making salts, even if that had occurred to me as an otherwise reasonable way forward.

14. For the reasons described above, it would not have been obvious to me to convert a peptidyl boronic acid such as TRI 50c or Rewinkel's compound 21 to a base addition salt for the purpose of making a pharmaceutical formulation. Similarly, I would not have predicted that the salts would have the enhanced stability demonstrated by the

data in examples 27 and 28 of the application. Indeed the improved stability came to me as an unexpected observation.

15. I would like also to comment on Rewinkel's compound 21. Rewinkel states that it is describing the results obtained in four classes of fibrinogen-derived LMW (low molecular weight) leads (page 1050, first full paragraph). In paragraph 2 of page 1054, it is then stated as follows:

> *"To stress the uniqueness of the boronic acid class, researchers replaced the guanidine group with non-basic moieties like the meta-cyanophenyl in **20** and the methoxy propyl in **21** [48, 49]."*

16. Thus, in referring to compounds 20 and 21, Rewinkel is merely describing work previously published by researchers in references 48 and 49. Reference 49 is Lee and describes the *meta*-cyanophenyl containing compound 20 whereas reference 48 is Deadman and describes methoxypropyl-containing compound 21. Rewinkel does not disclose the identity of the N-terminal group R of compound 21 but does disclose the following tripeptide sequence:

Dpa-Pro-boroMpg,

where Dpa is diphenylalanine, Pro is proline and boroMpg is boro-methoxy-propylglycine. The only such compound described as having been made in Deadman is compound 18 of Deadman:

Z-D-Dpa-Pro-boroMpg-OPin **(18)**,

where Z is benzoyloxycarbonyl and –OPin designates the pinanediol ester.

17. Since compound 21 of Rewinkel is a compound disclosed in Deadman and the only compound of Deadman having a matching tripeptide sequence is compound 18, I conclude that compound 21 of Rewinkel must be the pinanediol ester 18 of Deadman, and not a free boronic acid as illustrated in Rewinkel. The free boronic acid would nonetheless be the active species.

18. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001; and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Respectfully submitted,

Stephen Philip Marsden, Ph.D.

15TH July 2008

Date

Curriculum Vitae - Dr Stephen Marsden

Personal

Date/place of birth: 7th October 1969; Bury, Greater Manchester, UK

Career and Scientific Education:

August 2001 -	Reader in Organic Chemistry, University of Leeds
October 2000 -	Senior Lecturer in Organic Chemistry, Imperial College London
October 1994 -	Lecturer in Organic Chemistry, Imperial College, London
1993-4	Columbia University, New York NATO SERC Postdoctoral Fellowship Supervisor: Professor Samuel Danishefsky
1990-93	Imperial College of Science, Technology and Medicine Ph.D., Diploma of Imperial College Supervisor: Professor Steven Ley, F.R.S. Zeneca Postgraduate Scholar, 1992-3 Armstrong Medal of Imperial College
1987-90	Imperial College of Science, Technology and Medicine B.Sc. (Hons), 1st Class, Chemistry Associateship of the Royal College of Science Awarded Governor's Prize for Chemistry (IC), Neil Arnott Prize for Chemistry (University of London), Alfred Bader Prize in Organic Chemistry (IC), Barton Prize for Organic Chemistry (IC)

Membership of Professional Bodies

Member, Royal Society of Chemistry (MRSC, C. Chem.) (1990-)
Member, American Chemical Society (1994-)

Professional Honours

2008-10	Royal Society Industry Fellowship
1998	Meldola Prize and Medal, Royal Society of Chemistry
1996	Glaxo Wellcome Award for Innovative Organic Synthesis

Publications

41. 'Catalytic aza-Wittig Cyclisations for Heteroaromatic Synthesis'
S. P. Marsden, A. E. McGonagle, B. McKeever-Abbas, *Org. Lett.* **2008**, manuscript accepted.

40. 'Total Synthesis of the Indolizidine Alkaloid Tashiromine'
S. P. Marsden, A. D. McElhinney, *Beilstein J. Org. Chem.*, **2008**, 4:8

39. 'Isotopic Labelling for Determination of Enantiomeric Purity by ^{2}H NMR Spectroscopy'
H. Jackman, S. P. Marsden, P. Shapland, S. Barrett, *Org. Lett.*, **2007**, *8*, 5179-5182.

38. 'Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates'
S. P. Marsden, R. Newton, *J. Am. Chem. Soc.*, **2007**, *129*, 12600-12601.

37. 'Synthesis and Application of *P*-Stereogenic Phosphines as Superior Reagents in the Asymmetric Aza-Wittig Reaction'
C. E. Headley, S. P. Marsden, *J. Org. Chem.*, **2007**, *72*, 7185-7189.

36. 'Efficient Asymmetric Synthesis of Quaternary (*E*)-Vinylglycines by Deconjugative Alkylation of Dehydroamino Acids'
M. C. Jones, S. P. Marsden, D. M. Muñoz-Subtil, *Org. Lett.*, **2006**, *8*, 5509-5512.

35. 'A Concise, Convergent Total Synthesis of Monocerin'
J. H. Cassidy, C. N. Farthing, S. P. Marsden, A. Pedersen, M. Slater, G. Stemp, *Org. Biomol. Chem.*, **2006**, *4*, 4118-4126.

34. 'Concise Access to Indolizidine and Pyrroloazepine Skeleta via Intramolecular Schmidt Reactions of Azido 1,3-Diketones'
D. Lertpibulpanya, S. P. Marsden, *Org. Biomol. Chem.*, **2006**, *4*, 3498-3504.

33. 'Asymmetric aza-Wittig reactions: enantioselective of β-quaternary azacycles'
D. Lertpibulpanya, S. P. Marsden, I. Rodriguez Garcia, C. Kilner, *Angew. Chem. Int. Ed.*, **2006**, *45*, 5000-5002.

32. 'Reagent controlled asymmetric homologation of boronic esters by enantioenriched main-group chiral carbenoids'
P. R. Blakemore, S. P. Marsden, H. Vater, *Org. Lett.*, **2006**, *8*, 773-776.

31. 'Efficient synthesis of quaternary α-hydroxy acids by alkylation of α-ketoamide-derived dienediolates';
R. Newton, S. P. Marsden, *Synthesis*, **2005**, 3263-3270.

30. 'Deconjugation of dehydroamino acids: stereoselective synthesis of racemic (*E*)-vinyglycines
P. A. Alexander, S. P. Marsden, D. M. Muñoz-Subtil, J. C. Reader, *Org. Lett.*, **2005**, *7*, 5433-5436.

29. 'A concise total synthesis of tashiromine'
A. D. McElhinney, S. P. Marsden, *Synlett*, **2005**, 2528-2530.

28. 'Stereoselective synthesis of the octahydroisobenzofuran skeleton of the eunicellins'
T. Akindele, S. P. Marsden, J. G. Cumming, *Tetrahedron Lett.*, **2005**, 46, 7235-7238.

27. 'Synthesis of highly substituted allenylsilanes by alkylidenation of silylketenes'
S. P. Marsden, P. C. Ducept, *Beil. J. Org. Chem.*, **2005**, 1, 5.

26. 'Stereocontrolled assembly of tetrasubstituted tetrahydrofurans: a concise synthesis of virgatusin'
T. Akindele, S. P. Marsden, J. G. Cumming, *Org. Lett.*, **2005**, 7, 3685-3688.

25. 'Reagent-controlled stereoselective synthesis of lignan-related tetrahydrofurans'
S. M. Miles, S. P. Marsden, R. J. Leatherbarrow, W. J. Coates, *J. Org. Chem.*, **2004**, 69, 6874-6882.

24. 'A novel, stereoselective and convergent synthesis of aryltetralins'
S. M. Miles, S. P. Marsden, R. J. Leatherbarrow, W. J. Coates, *Chem. Commun.*, **2004**, 2292-2293.

23. 'Synthesis and bio-assay of RCM-derived Bowman-Birk inhibitor analogues'
S. M. Miles, R. J. Leatherbarrow, S. P. Marsden, W. J. Coates, *Org. Biomol. Chem.*, **2004**, 2, 281-283.

22. 'Inter- and intramolecular Diels-Alder/retro-Diels-Alder reactions of 4-silylated oxazoles'
P. C. Ducept, S. P. Marsden, *Arkivoc*, **2002**, 22-34.

21. 'Nickel-catalysed Synthesis of *C*-glycosides and Deoxysugars from Glycosyl Bromides';
S. K. Readman, S. P. Marsden, A. Hodgson, *Synlett*, **2000**, 1628-1630.

20. 'Chiral Vinyl Dioxazaborocines in Synthesis: Asymmetric Cuprate Additions to β-Boronyl Acrylates and Vinyl Sulfones';
C. N. Farthing, S. P. Marsden, *Tetrahedron Lett.*, **2000**, *41*, 4235-4238.

19. 'Enhanced Asymmetric Induction in Cycloadditions to Bridgehead-Chiral Vinyl Dioxazaborocines';
C. D. Davies, S. P. Marsden, E. S. E. Stokes, *Tetrahedron Lett.*, **2000**, *41*, 4229-4233.

18. ' Synthesis and Reactivity of 4-Silylated Oxazoles'
P. C. Ducept, S. P. Marsden, *Synlett*, **2000**, 692-694.

17. 'Epoxidation of Alkenes by Ozone Catalysed by Fe(TMP)Cl';
F.J. Waller, A.J. Bailey, W.P. Griffith, S. P. Marsden, E.H. Smith, *J. Mol. Catalysis.*, **2000**, *154*, 85-91.

16. 'The Total Synthesis of 5-N-Acetylardeemin and Amauromine: Practical Routes to Potential MDR Reversal Agents';
K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.*, **1999**, *121*, 11953-11963.

15. 'Efficient, General Synthesis of Silylketenes via an Unusual Rhodium Mediated Wolff Rearrangement';
S.P. Marsden, W.-K. Pang, *Chem. Commun.*, **1999**, 1199-1200.

14. 'Ozonolysis for the Preparation of High Oxidation-State Transition-Metal Complexes and the Crystal Structure of $[PPh_4]_2[Ru_2O(\mu\text{-}OCOEt)_2Cl_6]$'
A.J. Bailey, W. P. Griffith, S. P. Marsden, A. J. P. White, D. J. Williams, *J. Chem. Soc., Dalton Trans.*, **1998**, 3673-3678.

13. 'Chiral Vinyl Dioxazaborocines in Synthesis: Asymmetric Synthesis of 5-Substituted Δ^2-isoxazolines *via* Nitrile Oxide Cycloaddition';
C.D. Davies, S. P. Marsden, E. S. E. Stokes, *Tetrahedron Lett.*, **1998**, *39*, 8513-8516.

12. 'Rhodium Catalysed Reactions of Silylated Diazoacetates: Stereoselective Synthesis of α-Silylated γ-Lactones *via* C-H Insertion';
S.P. Marsden, W.K. Pang, *Tetrahedron Lett.*, **1998**, *39*, 6077-6080.

11. 'Stereocontrolled Polyol Synthesis *via* C-H Insertion Reactions of Silicon Tethered Diazoacetates';
S.N. Kablean, S.P. Marsden, A.M. Craig, *Tetrahedron Lett.*, **1998**, *39*, 5109-5112.

10. 'Stereoselective Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans by an Allyl Silane Metathesis - Nucleophilic Addition Sequence';
J.H. Cassidy, S.P. Marsden, G. Stemp, *Synlett*, **1997**, 1411-1413.

9. 'Organic Halides';
S.P. Marsden, *Contemp. Org. Synth.*, **1997**, *4*, 118-135.

8. 'A Novel, Stereocontrolled Synthesis of 1,2-*trans*-Cyclopropanes: Cyclopropyl boronate Esters as Partners in Suzuki Couplings with Aryl Halides ';
J. P. Hildebrand, S. P. Marsden, *Synlett,* **1996**, 893-894.

7. 'Organic Halides';
S.P. Marsden, *Contemp. Org. Synth.*, **1996**, *3*, 133-150.

6. 'An Application of Glycals to the Synthesis of Oligosaccharides: A Convergent Total Synthesis of Sialyl Lewis Antigen X and Higher Congeners';
S.J. Danishefsky, J. Gervay, J.M. Peterson, F.E. McDonald, K. Koseki, D.A. Griffith, T. Oriyama, S.P. Marsden, *J. Am. Chem. Soc.*, **1995**, *117*, 1940-1953.

5. 'Total Synthesis of Amauromine and 5-N-Acetylardeemin. A Concise, Stereoselective Approach to the Hexahydropyrroloindole Family of Alkaloids';
S.P. Marsden, K.M. Depew, S.J. Danishefsky *J. Am. Chem. Soc.*, **1994**, *116*, 11143-11144.

4. 'Tetrapropylammonium perruthenate, Pr_4N^+ RuO_4^-, TPAP: Catalytic Oxidant for Organic Synthesis';
S.V. Ley, J. Norman, W.P. Griffith, S.P. Marsden *Synthesis*, **1994**, 639-666.

3. 'Studies Towards the Total Synthesis of Rapamycin: Preparation of the Cyclohexyl C33-C42 Fragment and Further Coupling to Afford the C22-C42 Carbon Unit'
C. Kouklovsky, S.V. Ley, S.P Marsden *Tetrahedron Lett.*, **1994**, *35*, 2091-2094.

2. 'Studies Towards the Total Synthesis of Rapamycin: A Convergent and Stereoselective Synthesis of the C22-C32 Carbon Framework'
J.C. Anderson, S.V. Ley, S.P. Marsden *Tetrahedron Lett.*, **1994**, *35*, 2087-2090.

1. 'Diastereoselective and Enantioselective Formation of Quaternary Carbon Centers *via* the Intramolecular Heck Reaction: the Influence of the Coordination state of the Palladium Catalyst'
S. V. Ley, S. P. Marsden, *Chemtracts: Organic Chemistry*, **1993**, *6*, 23-6.

Book chapters

1. 'Product class 9: enones', in Science of Synthesis (2005), Volume 26, pp1045-1121.

Patents

1. 'Synthesis and Biological Activity of Analogs of *N*-Acetylardeemin for Use as Antitumor Agents' S. Danishefsky, K. Depew, S. P. Marsden, W. Bornmann, J. C. G. Woo, T.-C. Chou, J. Schkeryantz, A. Zatorski, PCT Int. Appl. (1997), WO 9718215.

Invited Lectures

89. Drug Discovery Unit, University of Dundee; 25/4/08
88. Syngenta, Jealott's Hill, Berkshire; 2/08
87. Department of Chemistry, University of Nottingham; 23/1/08
86. École Superieur de Physique et de Chimie Industrielles, Paris; 18/1/08
85. Institute for Chemistry of Natural Substances, Gif-sur-Yvette; 17/1/08
84. Institut Lavoisier de Versailles, Versailles; 16/1/08
83. Institute of Molecular Chemistry and Materials, Université Paris-Sud, Orsay; 15/1/08
82. Department of Chemistry and Organic Synthesis, École Polytechnique, Palaiseau, 14/1/08
81. Department of Chemistry, University of Cambridge; 19/11/07
80. Shasun Pharma Solutions, Northumberland; 26/10/07
79. Department of Organic Chemistry, University of Geneva; 11/10/07
78. Organic Chemistry: Perspectives on the 21st Century IV, St Lucia; 27/5-2/6/07 (invited)
77. 18th Lakeland Heterocyclic Symposium, Grasmere; 10-14/5/07 (invited)
76. 5th International Microwaves in Chemistry Conference, London; 18-20/4/07 (invited)
75. UCB Celltech, Cambridge; 31/1/07
74. Department of Chemistry, University of Oxford; 9/11/06
73. Department of Chemistry, University of Loughborough; 25/10/06
72. 232nd Meeting of the American Chemical Society, San Francisco, USA; 14/9/06(contributed)
71. 1st RSC Cornish Synthetic Organic Chemistry Symposium, Bude; 4/4/06 (Invited)
70. Eli Lilly Symposium, Eli Lilly, Windlesham; 26/1/06
69. Department of Chemistry, University of Glasgow; 16/1/06
68. Department of Chemistry, Imperial College; 29/11/05
67. Synthesis Section Symposium, University of Leeds; 9/11/05
66. Lilly Organic Chemistry Symposium, University of Reading; 1/11/05
65. Department of Chemistry, University of Sheffield; 11/5/05

64. AstraZeneca Pharmaceuticals, Alderley Park; 22/3/05

63. Department of Chemistry, University of Liverpool; 24/11/04

62. Department of Chemistry, Uppsala University, Sweden; 30/8/04

61. KaroBio, Stockholm, Sweden; 30/8/04

60. 1st Anglo-American Conference on Organic Synthesis, Edinburgh; 27-31/8/04 (Invited)

59. Department of Chemistry, University of Glasgow; 13/5/04

58. Department of Chemistry, University of Nottingham; 24/3/04

57. Department of Chemistry, University of Bristol; 9/3/04

56. Celltech, Slough; 22/1/04

55. Organic Chemistry: Perspectives on the 21st Century III, Heron Island; 3-7/11/03 (Invited)

54. Astex Technologies, Cambridge; 17/10/03

53. Department of Pure and Applied Chemistry University of Strathclyde, Glasgow; 15/10/03

52. RSC Heterocyclic Group Meeting, Novartis Research Centre, Horsham; 24/9/03 (Invited)

51. Maybridge Chemicals, Tintagel; 5/9/03

50. Organon, Newhouse, Lanarkshire; 3/9/03

49. RSC Perkin Division North of England meeting, University of Newcastle, 31/3/03 (Invited)

48. White Rose Chemistry Symposium, University of York, 11/12/02

47. Department of Chemistry, University of Warwick; 1/11/02

46. 224th Meeting of the American Chemical Society, Boston, USA (contributed); 20/8/02

45. Department of Chemistry, California Institute of Technology, Pasadena, USA; 16/8/02

44. Roche Biosciences, Palo Alto, USA; 13/8/02

43. Department of Chemistry, University of York; 17/1/02

42. Department of Chemistry, University of Manchester; 13/12/01

41. Syngenta, Basle, Switzerland; 18/10/01 (one of six Syngenta lecturers per year)

40. Celltech Chiroscience, Cambridge; 20/6/2001

39. Eli Lilly Research, Windlesham, Surrey; 29/5/2001

38. Department of Chemistry, University of Durham; 16/5/2001

37. Merck Sharp and Dohme Research Laboratories, Harlow; 15/2/2001

36. Department of Chemistry, University College, London; 1/11/2000

35. Traef for Organisk Kemi Studerende, Copenhagen, Denmark (plenary); 27/10/2000

34. Glaxo Wellcome, Stevenage, Herts.; 25/10/2000

33. RSC Perkin Division meeting, London; 24/10/2000

33. 220th Meeting of the American Chemical Society, Washington DC, USA (contributed); 20-24/8/2000

32. 7th Annual Imperial College Organic Chemistry Symposium; 19/5/2000

31. Meldola Medal lecture, at RSC Perkin Division meeting, London; 10/2/2000

30. Royal Society of Chemistry Heterocyclic Group, January Meeting , King's College; 7/01/2000

29. Department of Chemistry, University of Leicester; 19/10/99

28. Zeneca Pharmaceuticals, Alderley Park; 28/9/99

27. Knoll Pharmaceuticals, Nottingham; 13/7/99

26. Proteus, Macclesfield; 9/7/99

25. SmithKline Beecham, Tonbridge; 19/5/99

24. Organon, Newhouse, Lanarkshire; 27/4/99

23. Department of Chemistry, University of Leeds; 10/3/99

22. Department of Chemistry, University of Cambridge; 8/3/99

21. Faculty of Organic Chemistry, University of Salamanca, Spain; 15/1/99

20. Department of Chemistry, University of Bath; 26/11/98

19. Department of Chemistry, University of Sussex; 9/11/98

18. Department of Chemistry, University of Sheffield; 14/10/98

17. British Biotech Pharmaceuticals, Oxford; 26/8/98

16. Astra Charnwood, Loughborough, Leics.; 5/8/98

15. 5th Annual Imperial College Organic Chemistry Symposium; 25/6/98

14. Department of Chemistry, University of Liverpool; 6/5/98

13. Department of Chemistry, University of Birmingham; 17/3/98

12. Pfizer Central Research, Sandwich, Kent; 3/3/98

11. Department of Chemistry, University of Loughborough; 9/2/98

10. RSC Mid-Anglia Section, Roche Products, Welwyn Garden City; 4/2/98

9. Department of Chemistry, Queen Mary and Westfield College, London; 12/11/97

8. Zeneca Agrochemicals, Jealotts Hill, Berkshire; 25/9/97

7. School of Chemical Sciences, University of East Anglia, Norwich; 29/5/97

6. "21st Century Heterocyclic Synthesis " (Plenary speaker), University of Sunderland; 7/5/97

5. GlaxoWellcome Research and Development, Dartford, Kent; 20/3/97

4. SmithKline Beecham Pharmaceuticals, Harlow, Essex; 12/3/97

3. Department of Chemistry, University of Nottingham; 12/2/97

2. Eli Lilly Research, Windlesham, Surrey; 3/12/96

1. "Semaine d'Etudes de Chimie Organique XXXII" (Plenary speaker), Lyon, France; 1/6/95

Session chair at International Conference

Invited chair for session on "Proteins, Peptides, Amino Acids and Enzyme Inhibitors" (invitee: Dr Rob Larsen, Amgen, chair of organic section), 232nd ACS National Meeting, San Francisco, 14/9/06